# Package 'lrgpr'

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Title lrgpr
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<b>Description</b> Fit a Low Rank Gaussian Process Regression (LRGPR) / Linear Mixed Model (LMM) for large datasets. These models are widely used in statistical genetics as a test of association while correcting for the confounding effects of kinship and population structure.
<b>Depends</b> R (>= 3.0.0), methods, Rcpp, RcppGSL, RcppProgress, MASS,parallel, doParallel, formula.tools, BH, bigmemory (>= 4.4.7),aod
LinkingTo Rcpp, RcppGSL
<pre>URL http://lrgpr.r-forge.r-project.org/</pre>
License GPL (>= 2)
Collate 'genericFunctions.R' 'lrgpr.R' 'plink.R'
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AIC.lrgpr

 $Akaike's\ Information\ Criterion\ (AIC)$ 

### Description

AIC for model fit by lrgpr

### Usage

```
AIC.lrgpr(object, ..., k = 2)
```

```
object model fit with lrgpr
... other arguments
k for compotability, not used
```

BIC.lrgpr 3

BIC.lrgpr

Bayesian Information Criterion (BIC)

### Description

```
BIC for model fit by {\tt lrgpr}
```

### Usage

```
BIC.lrgpr(object, ...)
```

### Arguments

```
object model fit with lrgpr
... other arguments
```

```
coefficients.lrgpr Extract Model Coefficients
```

### Description

Coefficients estimated with lrgpr

### Usage

```
coefficients.lrgpr(object)
```

```
object model fit with lrgpr
... other arguments
```

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convertToBinary

Convert ASCII to binary file

### Description

'convertToBinary' converts TPED/DOSAGE/GEN files to binary format

### Usage

```
convertToBinary(filename, filenameOut, format)
```

### **Arguments**

```
filename file to be converted

filenameOut name of binary file produced

format specify 'TPED', 'DOSAGE' or 'GEN'
```

#### **Details**

- TPED: plink file can be in either -recode or -recode12 format
- DOSAGE: file follows plink format: http://pngu.mgh.harvard.edu/~purcell/plink/dosage.shtml

#### Example:

```
SNP A1 A2 F1 I1 F2 I2 F3 I3
rs0001 A C 0.98 0.02 1.00 0.00 0.00 0.01
rs0002 G A 0.00 1.00 0.00 0.00 0.99 0.01
where the F* values correspond to the dosage values
```

• GEN: file follow OXFORD format

```
cooks.distance.lrgpr
```

Regression Deletion Diagnostics

### Description

Basic quantities for regression deletion diagnostics from fit of lrgpr

#### Usage

```
cooks.distance.lrgpr(model,
  infl = lm.influence(model, do.coef = FALSE),
  res = weighted.residuals(model),
  sd = sqrt(deviance(model)/df.residual(model)),
  hat = infl$hat, ...)
```

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### **Arguments**

model	model fit with lrgpr
infl	influence structure as returned by lm.influence
res	residuals
sd	standard deviation to use
hat	hat values
	other arguments

criterion.lrgpr

Compute AIC/BIC/GCV for lrgpr() model as rank changes

### **Description**

'criterion.lrgpr' evaluate information criteria to select an optimal rank

### Usage

```
criterion.lrgpr(formula, features, order, rank = c(seq(1, 10), seq(20, 100, by = 10)), seq(200, 1000, by = 100)))
```

### Arguments

formula standard linear modeling syntax as used in 'lm'

features matrix from which the SVD is performed

order sorted indices of features. When rank is 10, decomp = svd(X[,order[1:10]])

rank array with elements indicating the number of confounding covariates to be used in the random effect.

#### See Also

```
plot.criterion.lrgpr, cv.lrgpr
#'
```

### **Examples**

```
n = 300
p = 5000
X = matrix(sample(0:2, n*p, replace=TRUE), nrow=n)
dcmp = svd(X)
# simulate response
h_sq = .8
eta = dcmp$u[,1:2] %*% rgamma(2, 2, 1)
error_var = (1-h_sq) / h_sq * var(eta)
```

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```
y = eta + rnorm(n, sd=sqrt(error_var))
# Get ordering based on marginal correlation
i = order(cor(y, X)^2, decreasing=TRUE)
# Fit AIC / BIC / GCV based on degrees of freedom
fit = criterion.lrgpr( y ~ 1, features=X, order=i)
plot.criterion.lrgpr(fit)
```

cv.lrgpr

Cross-validation for LRGPR

#### **Description**

'cv.lrgpr' fits cross-validation for multiple ranks of the LRGPR

### Usage

```
cv.lrgpr(formula, features, order, nfolds = 10,

rank = c(seq(0, 10), seq(20, 100, by = 10), seq(200, 1000, by = 100)),

nthreads = 1)
```

#### **Arguments**

formula standard linear modeling syntax as used in 'lm'

features matrix from which the SVD is performed

order sorted indices of features. When rank is 10, decomp = svd(X[,order[1:10]])

nfolds number of training sets

rank array with elements indicating the number of confounding covariates to be used in the random effect.

nthreads number of threads to be used

### **Examples**

```
n = 300
p = 5000
X = matrix(sample(0:2, n*p, replace=TRUE), nrow=n)

dcmp = svd(X)

# simulate response
h_sq = .8
eta = dcmp$u[,1:2] %*% rgamma(2, 2, 1)
error_var = (1-h_sq) / h_sq * var(eta)
y = eta + rnorm(n, sd=sqrt(error_var))

# Get ordering based on marginal correlation
```

df.residual.lrgpr 7

```
i = order(cor(y, X)^2, decreasing=TRUE)
# Fit cross-validation
fit = cv.lrgpr( y ~ 1, features=X, order=i)
plot.cv.lrgpr(fit)
```

```
df.residual.lrgpr Residual Degrees-of-Freedom
```

### **Description**

Residual df from fit of lrgpr

### Usage

```
df.residual.lrgpr(object, ...)
```

### Arguments

```
object model fit with lrgpr
... other arguments
```

error.bar

Plot Error Bars

### Description

Plot error bars for a confidence interval

### Usage

```
error.bar(x, y, upper, lower = upper, length = 0.1, ...)
```

```
x x-axis position
y y-axis position
upper height of bar above y
lower height of bar below y
length horizontal length of the error bar
... arguments for arrows(...)
```

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getAlleleFreq

Calculate allele frequency

### **Description**

Calculate allele frequency

### Usage

```
getAlleleFreq(X, nthreads = detectCores(logical = TRUE))
```

### Arguments

X matrix where each column is a marker coded 0,1,2 or with dosage values in this

range

nthreads number of threads to use

### Description

EValuate variance for each column

### Usage

```
getAlleleVariance(X,
  nthreads = detectCores(logical = TRUE))
```

### Arguments

X matrix where each column is a marker

nthreads number of threads to use

getMissingCount 9

	~
getMissingCount	Count missing values

### **Description**

Count missing values

### Usage

```
getMissingCount(X,
  nthreads = detectCores(logical = TRUE))
```

### **Arguments**

X matrix where each column is a marker

nthreads number of threads to use

glmApply Fit standard linear or logistic model for many markers

### Description

'glmApply' is analogous to 'lrgprApply', but fits standard linear or logistic models for many markers

### Usage

```
glmApply(formula, features, terms = NULL,
  family = gaussian(), useMean = TRUE,
  nthreads = detectCores(logical = TRUE),
  univariateTest = TRUE, multivariateTest = FALSE,
  verbose = FALSE)
```

formula	standard linear modeling syntax as used in 'lm'. SNP is a place holder for the each successive column of features
features	a matrix where the statistical model is evaluated with SNP if formula replace by each column successively
terms	indices of the coefficients to be tested. The indices corresponding to SNP are used if terms is not specified
family	gaussian() for a continuous response, and binomial() to fit a logit model for a binary response

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useMean if TRUE, replace missing entries with column mean. Otherwise, do not evaluate the model for that column

nthreads number of to use for parallel execution

univariateTest

perform univariate hypothesis test for each response for each feature in the loop variable

multivariateTest

perform multivariate hypothesis test for each response (if more than one) for each feature. Note that the runtime is cubic in the number of response variables

verbose print additional information

#### **Examples**

```
# Generate data
n = 100
p = 500
X = matrix(sample(0:2, n*p, replace=TRUE), nrow=n)
y = rnorm(n)
sex = as.factor(sample(1:2, n, replace=TRUE))
# Fit model for all markers
pValues = glmApply( y ~ sex + sex:SNP, features=X, terms=c(3,4))
# Multivariate model
n = 100
p = 1000
m = 10
Y = matrix(rnorm(n*m), nrow=n, ncol=m)
X = matrix(rnorm(n*p), nrow=n, ncol=p)
res = glmApply( Y ~ SNP, features = X, terms=2, multivariateTest=TRUE)
# p-values for univariate hypothesis test of each feature against
# each response
res$pValues
# p-values for multivariate hypothesis test of each feature against
# all responses are the same time
# returns the results of the Hotelling and Pillai tests
res$pValues_mv
# The multivariate test for X[,1]
res$pValues_mv[1,]
# The result is the same as the standard tests in R
fit = manova(Y \sim X[,1])
summary(fit, test="Hotelling-Lawley")
summary(fit, test="Pillai")
```

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```
influence.lrgpr Regression Diagnostics
```

### Description

Basic quantities for regression diagnostics from fit of lrgpr

### Usage

```
influence.lrgpr(model, ...)
```

### Arguments

```
model model fit with lrgpr
... other arguments
```

```
leverage.lrgpr
```

Regression Diagnostics

### Description

Basic quantities for regression diagnostics from fit of lrgpr

### Usage

```
leverage.lrgpr(object)
```

### **Arguments**

```
object model fit with lrgpr
```

```
lm.influence.lrgpr Regression Diagnostics
```

### Description

Basic quantities for regression diagnostics from fit of lrgpr

### Usage

```
lm.influence.lrgpr(object, ...)
```

```
object model fit with lrgpr
... other arguments
```

loss.lrgpr

logLik.lrgpr

Extract Log-Likelihood

### Description

Log-Likelihood for model fit by lrgpr

### Usage

```
logLik.lrgpr(object, ...)
```

### Arguments

```
object model fit with lrgpr
... other arguments
```

loss.lrgpr

Loss function

### Description

Compare observed and fitted response under some loss function

### Usage

```
loss.lrgpr(y, yhat, family)
```

### Arguments

y observed response yhat fitted response

family "gaussian" or "binomial"

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lrgpr	Fit a Low Rank Gaussian Process Regression (LRGPR) / Linear Mixed Model (LMM)

### Description

'lrgpr' is used to fit LRGPR/LMM models that account for covariance in response values, but where the scale of the covariance is unknown. Standard linear modeling syntax is used for the model specification in addition to a covariance matrix or its eigen-decomposition.

### Usage

```
lrgpr(formula, decomp,
  rank = max(length(decomp$d), length(decomp$values)),
  delta = NULL, nthreads = detectCores(logical = TRUE),
  W_til = NULL, scale = TRUE)
```

### Arguments

formula	standard linear modeling syntax as used in 'lm'
decomp	eigen-decomposition produced from eigen(K), where K is the covariance matrix. Or singular value decomposition $\operatorname{svd}(X[,1:100])$ based on a subset of markers
rank	decomposition is truncated to the first rank eigen-vectors
delta	ratio of variance components governing the fit of the model. This should be estimated from a previous evaluation of 'lm' on the same response and eigendecomposition
nthreads	number of threads to use for parallel execution
W_til	markers used to construct decomp that should now be removed from costruction of decomp. This is the proximal contamination term of Listgarten, et al. (2012)
scale	should W_til be scaled and centered

#### Value

regression coefficients for each covariate
p-values from Wald test of each coefficient
standard deviation of each coefficient estimate
variance component
$\sigma_e^2$
corresponding to the residual error
variance component
$\sigma_a^2$
corresponding the scale of the covariance, K

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delta ratio of variance components:

 $\sigma_e^2/\sigma_a^2$ 

rank the rank of the random effect logLik log-likelihood of the model fit

fitted.values

estimated response values: y\_hat

alpha BLUP of the random effect

Sigma variance-covariate matrix of estimate of beta
hii diagonals of the matrix H such that y\_hat = Hy

y responses x design matrix

df effective degrees of freedom: trace(H) based on Hoffman (2013)

residuals residuals of model fit: y - y\_hat
AIC Akaike information criterion
BIC Bayesian information criterion
GCV generalized cross-validation
eigenVectors eigen-vectors in decomp
eigenValues eigen-values in decomp

df.residual n-ncol(X)

rank of decomposition used, where only non-negative eigen/singular values are

considered

#### Details

'lrgpr' fits the model:

$$y = X\beta + \alpha + \epsilon$$

$$\alpha \sim N(0, K\sigma_a^2)$$

$$\epsilon \sim N(0, \sigma_e^2)$$

where

$$\delta = \sigma_e^2/\sigma_a^2$$

In practice the eigen-decomposition of K, and not K itself is required. The rank can be set to use only eigen-vectors 1:rank in the model.

This package allows hypothesis tests of single coefficients using fit\$p.values which fits a Wald test. Composite hypothesis tests of multiple coefficients are performed with wald(fit, terms=1:3).

Note that likelihood ratio tests with linear mixed models do not perform well and the resulting p-values often do not follow a uniform distribution under the null (Pinheiro and Bates, 2000). We strongly advise against using it with this model.

'lrgpr' uses the algorithm of Lippert, et al. (2011).

See Hoffman (2013) for an interpretation of the linear mixed model.

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#### References

Kang, H. M., et al. (2010) Variance component model to account for sample structure in genome-wide association studies. \_Nature Genetics\_ 42, 348-54

Lippert, C., et al. (2011) FaST linear mixed models for genome-wide association studies. \_Nature Methods\_ 9, 525-26

Listgarten, J., et al. (2012) Improved linear mixed models for genome-wide association studies. \_Nature Methods\_ 8, 833-5

Rasmussen, C. E. and Williams, C. K. I. (2006) Gaussian processes for machine learning. MIT Press

Pinheiro, J. C. and Bates, D. M. (2000) Mixed-Effects Models in S and S-PLUS. Springer, New York

Hoffman, G. E. (2013) Correcting for Population Structure and Kinship Using the Linear Mixed Model: Theory and Extensions. \_PLoS ONE\_ 8(10):e75707

### See Also

'wald', 'lrgprApply'

#### **Examples**

```
# Generate random data
set.seed(1)
n < -200
v <- rnorm(n)
K <- crossprod( matrix(rnorm(n*1000), ncol=n) )</pre>
age <- rpois(n, 50)
sex <- as.factor(sample(1:2, n, replace=TRUE))</pre>
decomp <- eigen(K)</pre>
# Fit the model
fit <- lrgpr( y ~ sex + age, decomp)
# Print results
fit
# Print more detailed results
summary(fit)
# P-values for each covariate
fit$p.values
# Visualize fit of the model like for 'lm'
par(mfrow=c(2,2))
plot(fit)
# Composite hypothesis test using Wald's test
# Joint test of coefficients 2:3
wald( fit, terms=2:3)
```

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72 22 2	Fit a Low Rank Gaussian Process Regression (LRGPR)/Linear Mixed Model (LMM) for many markers
---------	---

### Description

'lrgprApply' is used to fit LRGPR/LMM models that account for covariance in response values, but where the scale of the covariance is unknown. It returns p-values equivalent to the results of lrgpr() and wald(), but is designed to analyze thousands of markers in a single function call.

### Usage

```
lrgprApply(formula, features, decomp, terms = NULL,
  rank = max(length(decomp$d), length(decomp$values)),
  map = NULL, distance = NULL, dcmp_features = NULL,
  W_til = NULL, scale = TRUE, delta = NULL,
  reEstimateDelta = FALSE,
  nthreads = detectCores(logical = TRUE),
  verbose = FALSE)
```

formula	standard linear modeling syntax as used in 'lm'. SNP is a place holder for the each successive column of features
features	a matrix where the statistical model is evaluated with SNP if formula replace by each column successively
decomp	eigen-decomposition produced from eigen(K), where K is the covariance matrix. Or singular value decomposition $svd(features[,1:100])$ based on a subset of markers
terms	indices of the coefficients to be tested. The indices corresponding to SNP are used if terms is not specified
rank	decomposition is truncated to the first rank eigen-vectors
map	p x 2 matrix where each entry corresponds to a marker in features. First column is the marker names, second columns is the genetic or physical location
distance	size of the proximal contamination window in units specifed by map.
dcmp_feature	es
	the indices in features of the markers used to construct dcmp
W_til	markers used to construct decomp that should now be removed from costruction of decomp. This is the proximal contamination term of Listgarten, et al. (2012)
scale	should W_til be scaled and centered
delta	ratio of variance components governing the fit of the model. This should be estimated from a previous evaluation of 'lm' on the same response and eigendecomposition

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```
reEstimateDelta
```

should delta be re-estimated for every marker. Note: reEstimateDelta=TRUE is

much slower

nthreads number of to use for parallel execution

verbose print extra information

### **Examples**

```
# Generate data
n = 100
p = 500
X = matrix(sample(0:2, n*p, replace=TRUE), nrow=n)
y = rnorm(n)
sex = as.factor(sample(1:2, n, replace=TRUE))

K = tcrossprod(matrix(rnorm(n*n*3), nrow=n))
decomp = eigen(K, symmetric=TRUE)

# Fit null model
fit = lrgpr( y ~ sex, decomp)

# Fit model for all markers
pValues = lrgprApply( y ~ sex + sex:SNP, features=X, decomp, terms=c(3,4), delta=fit$delta)
```

```
plot.criterion.lrgpr
```

Plot AIC/BIC/GCV values for lrgpr() model as rank changes

### **Description**

'plot.criterion.lrgpr' plots the criteria returned by 'criterion.lrgpr'

### Usage

```
plot.criterion.lrgpr(x, col = rainbow(3), ...)
```

### Arguments

```
x list returned by 'criterion.lrgpr'col array of 3 colors... other arguments
```

### See Also

criterion.lrgpr

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```
plot.cv.lrgpr
```

Plot Results of Cross-validation

### **Description**

Plot results of 'cv.lrgpr', which fits cross-validation for multiple ranks of the LRGPR

#### Usage

```
plot.cv.lrgpr(x,
   ylim = c(min(x$cve - x$cvse), max(x$cve + x$cvse)),
   xlim = range(x$rank), pch = 20, col = "red",
   main = "Cross validation", xlab = "# of markers used",
   ylab = "Cross validation error", ...)
```

#### **Arguments**

```
Х
                  result of cv.lrgpr
                  limits of y-axis
ylim
                  limits of x-axis
xlim
pch
                  pch
col
                  col
main
                  main
xlab
                  xlab
ylab
                  ylab
                  other parameters fed to plot()
```

```
plot.lrgpr
```

Plot Diagnostics for an lrgpr Object

### **Description**

Six plots (selectable by \"which\") are currently available: a plot of residuals against fitted values, a Scale-Location plot of sqrt(| residuals |) against fitted values, a Normal Q-Q plot, a plot of Cook's distances versus row labels, a plot of residuals against leverages, and a plot of Cook's distances against leverage/(1-leverage). By default, the first three and \"5\" are provided.

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### Usage

```
plot.lrgpr(x, which = c(1L:3L, 5L),
   caption = list("Residuals vs Fitted", "Normal Q-Q", "Scale-Location", "Cook's of panel = if (add.smooth) panel.smooth else points,
   sub.caption = NULL, main = "",
   ask = prod(par("mfcol")) < length(which) && dev.interactive(),
   ..., id.n = 3, labels.id = names(residuals(x)),
   cex.id = 0.75, qqline = TRUE, cook.levels = c(0.5, 1),
   add.smooth = getOption("add.smooth"),
   label.pos = c(4, 2), cex.caption = 1)</pre>
```

### **Arguments**

X	lrgpr object.
which	if a subset of the plots is required, specify a subset of the numbers \"1:6\".
caption	captions to appear above the plots; \"character\" vector or \"list\" of valid graphics annotations, see \"as.graphicsAnnot\". Can be set to \"""\" or \"NA\" to suppress all captions.
panel	panel function. The useful alternative to \"points\", \"panel.smooth\" can be chosen by \"add.smooth = $TRUE$ \".
sub.caption	common title-above the figures if there are more than one; used as \"sub\" (s.\"title\") otherwise. If \"NULL\", as by default, a possible abbreviated version of \"deparse(x\$call)\" is used.
main	title to each plot-in addition to \"caption\".
ask	logical; if \"TRUE\", the user is _ask_ed before each plot, see \"par(ask=.)\".
	other parameters to be passed through to plotting functions.
id.n	number of points to be labelled in each plot, starting with the most extreme.
labels.id	vector of labels, from which the labels for extreme points will be chosen. \"NULL\" uses observation numbers.
cex.id	magnification of point labels.
qqline	logical indicating if a \"qqline()\" should be added to the normal Q-Q plot.
cook.levels	levels of Cook's distance at which to draw contours.
add.smooth	logical indicating if a smoother should be added to most plots; see also \"panel\" above.
label.pos	positioning of labels, for the left half and right half of the graph respectively, for plots 1-3.
cex.caption	controls the size of \"caption\".

### See Also

```
plot.lm
```

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### Description

Predict response values after training with lrgpr. Leaving  $X_{test}$  amd  $K_{test}$  as NULL returns the fitted values on the training set

### Usage

```
predict.lrgpr(object, X_test = NULL, K_test = NULL, ...)
```

### **Arguments**

```
object model fit from lrgpr on training samples

X_test design matrix of covariates for test samples

K_test covariance matrix between samples in the test set and training set

... other arguments
```

```
print.lrgpr Print Values
```

### **Description**

Print details for fit from lrgpr

### Usage

```
print.lrgpr(x, ...)
```

```
x model fit from lrgpr... other arguments
```

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```
 \begin{array}{c} \texttt{print.summary.lrgpr} \\ \textbf{\textit{Object Summaries}} \end{array}
```

### **Description**

Print summary for fit from lrgpr

### Usage

```
print.summary.lrgpr(x, ...)
```

### **Arguments**

```
x model fit from lrgpr... other arguments
```

read.fam

Read plink FAM/TFAM files

#### **Description**

Read FAM/TFAM file into a dataframe. This function is the same as read.tfam

### Usage

```
read.fam(file)
```

### **Arguments**

file

location of FAM/TFAM file

read.tfam

Read plink FAM/TFAM files

### **Description**

Read FAM/TFAM file into a dataframe. This function is the same as read.fam

#### Usage

```
read.tfam(file)
```

### **Arguments**

file

location of FAM/TFAM file

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```
residuals.lrgpr Extract Model Residuals
```

### Description

Residuals fitted with lrgpr

### Usage

```
residuals.lrgpr(object, type = "working", ...)
```

### Arguments

. . .

```
object model fit with lrgpr
type the type of residual, but there is only one option here
```

```
rstandard.lrgpr Regression Deletion Diagnostics
```

other arguments

### Description

Basic quantities for regression deletion diagnostics from fit of lrgpr

### Usage

```
rstandard.lrgpr(model, ...)
```

```
model model fit with lrgpr
... other arguments
```

set\_missing\_to\_mean 23

```
set_missing_to_mean
```

Replace Missing Values with Mean

### Description

For each column, replace NA values with the column mean

### Usage

```
set_missing_to_mean(A)
```

### **Arguments**

Α

matrix

summary.lrgpr

Summarizing LRGPR / Linear Mixed Model Fits

### **Description**

Print summary for fit from lrgpr

### Usage

```
summary.lrgpr(object, ...)
```

### Arguments

```
object model fit from lrgpr
... other arguments
```

vcov.lrgpr

Calculate Variance-Covariance Matrix for a lrgpr Object

### **Description**

Returns the variance-covariance matrix of the main parameters of a fitted model object

### Usage

```
vcov.lrgpr(object, ...)
```

```
object model fit with lrgpr
... other arguments
```

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wald

Composite hypothesis test of multiple coefficients

### Description

'wald' performs a multi-dimensional Wald test against H0: beta\_i...beta\_j = 0 using the estimated coefficients and their variance-covariance matrix

### Usage

```
wald(fit, terms)
```

### Arguments

fit result of fitting with 'lrgpr'

terms indices of the coefficients to be tested

### **Details**

The Wald statistic is

$$\beta_h^T \Sigma_h^{-1} \beta_h \sim \chi_{|h|}^2$$

where

h

specifies the coefficients being tested and

h

is the number of entries

### See Also

'lrgpr'

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